



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Citron, et al.

Serial No.: 09/277,229

Group Art Unit No.: 1652

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Examiner: Manjuranath N. Rao

For: Beta Secretase Genes and Polypeptides

Docket No.: A-581

#22
6.9
8/4/03

DECLARATION UNDER 37 CFR 1.131

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

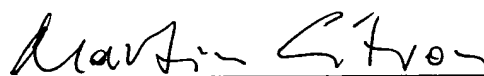
Sir:

I, Martin Citron, Ph.D., declare that:

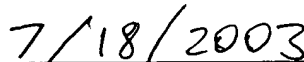
1. I have been employed by Amgen Inc. since 1997 and currently hold the title of Associate Director II;
2. I am an applicant of the referenced patent application and a co-inventor of the claimed subject matter set forth therein;
3. I have reviewed the Official Action directed to the referenced patent application dated January 24, 2003, and I understand that the claims have been rejected under 35 USC 102(e) as lacking novelty in view of SEQ ID Nos: 4 and 8 disclosed in U.S. Patent Nos. 6,420,534 B1 and 6,440,698 B1. I understand that the '534 patent and the '698 patent both have a priority date of 24 September 1998.
4. I was the head of the beta-secretase project at Amgen at the time the invention as claimed in the referenced patent application was made;
5. I worked together with the other named inventors and their assistants to identify the beta secretase gene and polypeptide;
6. A true copy of the human beta secretase DNA sequencing data we obtained, together with a translation of such DNA in all 3 reading frames is attached hereto as Exhibit A and the true and correct sequence of beta secretase is set forth in the second reading frame, with the start and stop positions indicated.

7. Although the dates have been redacted in Exhibit A, the data set forth therein was all obtained prior to September 24, 1998.

I further declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both (18 USC 1001), and may jeopardize the validity of the application or any patent issuing thereon.



Martin Citron, Ph.D.



Date

Please send all future correspondence to:

US Patent Operations/NAO
Dept. 4300, M/S 27-4-A
AMGEN INC.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

check: 2385 from: 1 to: 2965

B. Bennett
DNA=FHK004008-C3
Assembled by CS.

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MaxCuts: 4

[illegible]

I * V T L * N H F A F L S T G V H S -
R * H Y R I T S T L P F S P Q V S T P -

HincII
 SmaI
 AccI
 EcoRI TagI DrrI
 MneI SalI AflIII
 NruI HgaI MluI AceIII

241

 300

a P G P T A P R E Y R D * I R R P T R P Q -
b Q V Q L H L G S I A I E F V D P R V R S -
c R S N C T S V L S R L N S S T H A S A A -

[illegible]

a P A R E L R A A S W I M V A * A A N A A -
b P P G S C E P R A G L W W P E Q P T Q P -
c R P G A A S R E L D Y G G L S S O R S R -

[illegible]

```

a      A G A R S P C P C P R R R P P G G P G K -
b      Q E P G A L A P A R A A A R R G D Q G S -
c      R S P E P L P L P A P P P A G G T R E A -

```

[illegible]

```

a      P P P A R H A R P S Q P R R E P A P A A -
b      R H R P A M P A P P S P A G S P R P L P -
c      A T G P P C P P L P A P P G A R A R C P -

```

BamHI
 BstYI
 BsaNI
 BspEI
 BclGI
 481-----540

a Q A G R R R A D V A G S G S Q P L P C S -
b R L A A A V P M * R A P D P S L S P A P -
c G W P P P C R C S G L R I P A S P L L P -

```

a      R A L R I S P D R S P Q P G P G G W P R -
b      V L C G S P L T A L H S P D P G A G P G -
c      C S A D L P ' P L S T A R T R G L A Q G -

```

```

a      A L Q A L A S * C P Q A P S P E K P P A -
b      P C R P W R P D A P K L P L L R S H Q H -
c      P A G P G V L M P P S S L S * E A T S T -

```

```

a      P P R L G G R R Q G R T W A S A S P E G -
b      H P D L G A G A R D G R G P V R A Q R A -
c      T O T W G O A P G T D V G Q C E P R G P -

```

a P K A G A H H G P S P A L A P A V D G R -
b R R P G P T M A Q A L P W L L L W M G A L
c E G R G P P W P K P C P G S C C G W A R -

↓ start

FspI

781
 791
 801

a C S A A C P F H F A R H P A A F A L R P -
 b G V L P A H G T Q H G I R L P L R S G L -
 c E C C L P T A P S T A S F C F C A A A W -

HaeII
 BsaHI
 NarI
 BstAI
 Aval
 BsaI
 BstAI
 SapI
 RsaI
 941
 951

a G S R P P G A A A A P G D R R R A R G A -
 b G G A P L G L R L P R E T D E E P E P -
 c G A P P W G C G C P E R P T E S P R S P -

BsePI
 BsiEI
 BglI
 Bsu36I
 901
 960

a R P E G Q L C G D G G Q P E G Q V G A G -
 b G R R G S F V E M V D N L R G K S G Q G -
 c A G G A A L W R W W T T * G A S R G R A -

BsaAI
 MslI
 BclI
 HgaI
 961
 1020

a L L R G D D R G Q P P A D A Q H P G G Y -
 b Y Y V E M T V G S P P Q T L N I L V D D I L -
 c T T W R * P W A A P F R R S T S W W I Q -

BstAPI
 BtsI
 1021
 1080

a R Q Q * L C S G C C P P P L P A S L L P -
 b G N S F S L N F A V G A A P H P F L H R Y Y Q -

A A V T L Q W V L P P T P S C I A T T R -

1081
EcoNI
BsaNI
BspEI
BspGI
PvuII
Psp5II
GAGGCAGCTGTCTCCAGCAGATACCGGGACCTCCGGAGGGTGTGTATGTGCGCTACACCCA
CTCCGTGACACGCTGCTGTGTGGGCGCTCGAGGCTTCCTACACATACACCGGATGTGGGT

a E A A V Q H I P G P P E G C V C A L H P -
b R Q L S S T Y R D L R K G V Y V P Y T Q -
c G S C P A H T G T S G R V C M C P T P R -

1141
AceIII
SexAI
NcoI
GGGCAATGTGGGAGGGGAGCTGGGCAACCACTGGTAAAGCATCCCGCATGGCGGCAAGGT
CCCGTTCAACCTTCCTCCGACCGGCTGGGCTGGACCATTCGTAGGGGGTACCGGGGTGCA

a G Q V G R G A G H R P G K H P P W P Q R -
b G K W E G E L G T D L V S I P H G P N V -
c A S G K G S W A P T W * A S P M A P T S -

1201
EcoK12
BsrDI
TfiI
CACTGTGGGTGGCAACATGTCTGCCATCACTGAATCAGACAGTTCTTCATCAAGGGCTC
GTACACCGCACCGTTGTAAAGACCGTAGTCACTTAGTCTGTTCACAGAGTGTGTGGGAG

a H C A C Q H C C H * I R Q V L H Q R L -
b T V R A N I A A I T E S D K F F I N G S -
c L C V P T L L P S L N Q T S S S S T A P -

1261
BfiI
MreI
PleI
StuI
CAACTGGGAGGGCATCTCTGGGGCTGGGCTATGCTGAGATTCGACGGCTGAGACTCCT
GTTGACCGCTTCGGTAGGACCGGACCGGATAGACTCTTAACGGTCCGGACTGCTGAGCGA

a Q L G R H P G A G L C * D C Q A * R L P -
b N W E G I L G L A Y A E I A R P D D S L -
c T G K A S W G W P M L R L P G L T T P W -

1321
PleI
BpmI
SmaI
BsaXI
EarI
PstI
GGAGCGTTTCTTTGACTCTCTGGTAAAGCAGACCGGCTCCCAACCTCTTCTCCCTGCA
CCTCGGAAGCAACTGAGAGACCAATTCTGCTCGGTGCAAGGCTTGGACAGAGCGGACGT

a G A F L * L S G K A D P R S Q P L L P A -
b E P F F D S L V K Q T H V F N L F S L Q -

c S L S L T L W * S R P T F P T S S P C S -

MneI Eco57I

1381 -----+----- 1440

GGTTTGTGGTGGTGGCTTCCTCTCAACCAAGTCTGAAGTGGTGGCTCTCTGGGAGGGAG

CGAAGCAACCAAGCAAGGAGGGGGTGTGGTCAAGCTTCAGAGCCGGAGACAGGCTCCCTC

a A L W C W L P P Q P V * S A G L C R R E -

b L G A G F P L N Q S E V L A S V G G S -

c F V V L A S P S T S L K C W P L S E G A -

BsrGI BstZ17I

BclI TaqI TatI AccI

1441 -----+----- 1500

CATGATCATTTGGAGGTATCGACCACTGGCTGTACACAGGCAGTCTCTGGTATACACCCAT

GTACTAGTAACCTCCATAGCTGGTGAGCGACATGTGTCCGTACAGAGCCATATGTGGGTA

a H D H W R Y R P L A V H R Q S L V Y T H -

b M I I G G I D H S L Y T G S L W Y T P I -

c * S L E V S T T R C T Q A V S G I H P S -

BclI BstYI

1501 -----+----- 1560

CCGGCGGGAGTGGTATTATCGAGGTGATCATTTGTCCGGGTGGAGATCAATGGACAGCATCT

GGCGCGCCCTCACCATTAATACTCCACTAGTAACCGCGCCCTCTAGTTACCTGTCTAGA

a P A G V V L * G D H C A G G D Q W T G S -

b R R E W Y Y E V I I V R V E I N - G Q D L -

c G G S G I M R * S L C G W R S M D R I * -

TatI

1561 -----+----- 1620

GAAATGCACTGGCAAGGAGTACCACTATGACAGAGCCATTGTGGACAGTGGCAACCA

CTTTTACCTGACGTTCTCATGTTGATACTGTCTCGTAACACCTGTCAACCGTGGTGGTT

a E N G L Q G V Q L * Q E H C G Q W H H Q -

b K M D G K E Y N Y D K S I V ~~DESECAALPEN~~ -

c K W T A R S T T M T R A L W T V A P P T -

Tth111II PstI BseRI

1621 -----+----- 1680

CCCTGTGTTTGGCCCAAGAAAGTGTGTAAGCTGCAGTCAAAATCCATCAAGGCAGCCTCTC

GGAGCAAAACGGGTTCCTTTCACAACTTCGAAGTCACTTTAGGTAGTTCCGTGGCAGAG

a P S F A Q E S V * S C S Q I H Q G S L L -

b L R L P K K V F E A A V K S I K A A S S -

c F V C P R K C L K L Q S N P S R Q P P P -

BfaI PvuII

1581 CACGGAGAACTGTCCTGATGCTTTCTGGGCTAGGAGAGGAGCTGCTGTGCTTGGCAACACAG
-----+ 1741
GAGGCTTTCTCAAGGACTTACCAAGAGACCGANCTCTCTGAGAACACAGACCGCTTCTCTC

a H G E V P * W F L A R R A A G V L A S R -
b T E K F P D G F W L G E Q L V @ W Q A G -
c R R S S L M V S G * E S S W C A G K Q A -

Pf1MI XbaI
Tth1111I BstII BstEII

1741 CACCAACCCCTTGAACCTTTTCCCTGCTATCTCTCTCTTAAATGGGTGAGGTTACCA
-----+ 1801
GTGCTGGGAAACCTTGTAAAGGGTCACTAGACTGGAATCGCTTACCCACTTCCATGCTT

a H H P L E H F P S H L T D P N G * G Y Q -
b T T P W N I F P V I S L Y L M G E V T N -
c P P L G T F S Q S S H S T * W V R I P T -

BstAPI BspMI MscI

1801 CCAGTCTCTTCCGCATCAACATCTCTCCGACGCAATACCTGCGGCTCAGTGGAGATGTGGC
-----+ 1861
GGTCAGGAAGGGGTAGTGGTAGGAGGGGTGGTCTATGGACCGCGGTACCTTCTACACCG

a P V L P H H H P S A A I P A A S G R C G -
b Q S F R I T I L P Q Q Y L R P V E D V A -
c S P S A S P S F R S N T C G Q W K M W P -

AceIII
BscCI MslI

1861 CACGTCCCAAGAGGACTGTACAGTTTCCCATCTCCACGTCTTCCAGGCGACTGTAT
-----+ 1921
GTGCAGGGTCTCTGCTGACAACTGTTCACAGGCTAGAGTGTACGTAGGTGCGCGGTGACATA

a H V P R R L L Q V C H L T V I H G H C Y -
b T S Q D D @ Y K F A I S Q S S T G T V M -
c R P K T T V T S L P S H S H P R A L L W -

Hin4I ApeI

1921 GGGAGCTGTATCTCTGGAGGGCTTCTAGCTTGTCTTTGATCGGCGCGAAACGCAATTCG
-----+ 1981
CCCTCGGCAATAGTAACTTCCGAGATCCACAGAACTAGCGCGCGCTTTTGGCTTAACT

a G S C Y H G G L L R C L * S G P K T N W -
b G A V I M E G F Y V V F D R A R K R I G -
c E L L S W R A S T L S L I G P E N E L A -

HaeII BsiHVI
Eco47III ApeLI

1981 CTTTGGGTCTAGCGCTTGGCACTGTGACGATGCTTACGAGCGAGCGGTGCTAGGCGC
-----+ 2041

L C C Q R L P C A R * V Q D G S G G R P -
F A V S A D E V H D E F E T A A V E G P -
L L S A C A M C T M S S G R Q E W K A L -

F C H I G H G R L W L Q H S T D E V N
F V T L D M E D G Y N I P Q T D E S T
L S P W T W K T V A T T F H R Q N S Q P

P H D H S L C H G C H L R P L E A A T L -
L M T I A Y V M A A I A L F M L P L -
S * P * P M S W L P S A P S S C C H S A -

PHGVSVLPPLPAPAA*-LC-
LMVQWRRLRLRQQHDDFA-
SWCVSGAASAAACASSMMTLL-

* * E L P A E V R R P M G R R * R F P W -
D D I S L L K * G G P W A E D R D S P G -
M T S P C * S E E A H G Q K I E I P L D -

BsaXI
 HpaII MspI DdeII
 ↓ stop
 AATACACCTCTCCCTGGTTCCTTTGGTTCACAGTACGACACACAGATGGGACCTGTGGGCA
 2281 ----- 2340

TTGTTGTGGAGGCAOCCAAAGTGAACCAGTGTTCATCCTCTGTGTCTAACCGTGGACACCGGT

a T T P P W F T L V T S R R H R W H L W P -
b P H L R G S L W S Q V G D T D G T C G Q -
c H T S V V H F G E K * E T Q M A P V A R -

Psp5II
Bsu36I
BsiHKAII SimI

2341 GAGCAOCTCAGGACCOCTOCCCAOCCACCAATGCCCTGTGCTTGTATGGAGAGGAAAGG
-----+-----+-----+-----+-----+ 2400
CTCTGTGGAGTCTCTGGGAGGGGTGGGTGGTTTACGGAGACGGAACCTACCTCTTCTCTTTTCC

a E H L R T L P T H Q M P L P * W R R K R -
b S T S G P S P P T K C L C L D G E G K G -
c A P Q D P P H P P N A S A L M E K E K A -

2401 CTGGCAAGGTGGGTTCGAGGCACTGTACTGTAGGAAACAGAAAGCGAAGAGAGAGCA
-----+-----+-----+-----+-----+ 2460
GACCGTTCACCAOCCAAAGTTCCTTCATGACATCCTTTTCTTTCTCTTCTTTCTTCTTGT

a L A R W V P G T V P V G N R K E K K E A -
b W Q G G F Q G L Y L * E T E K R R K K H -
c G K V G S R D C T C R K Q K R E E R S T -

BstEII MseI Tth111II Eco57I
CTCTGTGGGGCAATACTCTTGTCTACCTCAATTTTAAGTGGGAAATTCCTGCTGCTTG
2461 -----+-----+-----+-----+-----+ 2520
GACAGCAOCCOCCCTTATGCAOCCAGTGGAGTTTAAATTCAGCCCTTTTACAGCAOAGAAC

a L C W R E Y S W S P Q I * V G K F C C L -
b S A G G N T L G H L K F K S G N S A A * -
c L L A G I L L V T S N L S R E I L L L E -

DraI
MseI
AAACTTCAGCCCTGAACCTTTGTCCACCATTCCTTTAAATTCCTCCACCCCAAGTATCT
2521 -----+-----+-----+-----+-----+ 2580
TTTCAGTCTGGGACTTGGAAACAGGTGGTAAGCAATTTAAGAGGTTGGCTTTTCATPACA

a K L Q P * T F V H H S F K F S N P K Y S -
b N F S P E P L S T I P L N S P T Q S I L -
c T S A L N L C P P F L * I L Q P K V F F -

ScaI
MseI TatI BspMI BstEII
TCTTTTCTAGTTTCAGAGTACTGGCCTCACAAGCGAGTTACTTGGGGTGTGTCCCTG
2581 -----+-----+-----+-----+-----+ 2640
ACAAAAGAAATCAAACTCTTCATGACCGTAGTGTGGCTCCAAATGGAAOCCGACACAGGGAC

a
'b
c

2641

a
b
c

2703

3

2761

a
b
c

2821

a
b
c

2882

a L Q I K Q * H H K F H K * S I F F T A F -
 b Y K * S N S I T N F T N K A F F S L H S -
 c T N K A I A S Q I S Q I K H F F H C I L -

TAGTGTGGTTTGTCCAAACTCATC

2941 -----+----- 2965

ATCAACACCAACAGGTTTGAGTAG

a * L W F V Q T H -
 b S C G L S K L I -
 c V V V C P N S -

Enzymes that do cut and were not excluded:

EcoK12	AccI	AceIII	AflIII	AloI	ApaI	ApalI	AvaI
BaeI	BamHI	EbsI	BciVI	BclI	BfaI	BfiI	EpnI
Bpu10I	BsaI	BsaAI	BsaHI	BsaWI	BsaXI	BscGI	BseRI
BegI	BsiEI	BsiHFAI	BsmI	BspEI	BspGI	BspMI	BsrEI
BsrDI	BsrFI	BsrGI	BstAPI	BstEII	BstXI	BstVI	BstZ17I
Bsu36I	BtsI	DraI	DrdI	DrdII	EagI	EaI	Eco47III
Eco57I	EcoNI	EcoRI	EcoRV	FspI	HaeII	HgaI	Hin4I
HincII	HindIII	KpnI	MluI	MneI	MscI	MseI	MslI
NarI	NcoI	NotI	NruI	PflMI	PleI	Psp5II	PstI
PvuII	RcaI	SacII	Sall	SapI	SbfI	ScaI	SexAI
SfiI	SimI	SmaI	StuI	TaqI	TatI	TfiI	Tth111II
VspI	XmnI						

Enzymes that do not cut:

AarI	AatII	AccI	AflII	AhdI	AscI	AvrII	EbvCI
Bce83I	BcgI	BglII	Bpli	Bpu1102I	BsaBI	BsbI	BsmBI
Bsp24I	Bsp111I	BssHII	BssSI	ClaI	DraIII	EciI	FseI
HaeIV	HgiEII	HpaI	MmiI	NdeI	NgoAIV	NheI	NsiI
NspI	NspV	PacI	Pfl1108I	PinAI	PneI	PmlI	PshAI
PvuI	RleAI	RsrII	SacI	SanDI	SgfI	SgrAI	SmlI
SnaBI	SpeI	SphI	SrfI	Sse8647I	SspI	SunI	SwaI
Tth111I	UbaLI	XbaI	XcmI	XhoI			

Enzymes excluded; MinCuts: 1 MaxCuts: 4

AccI	AluI	AlwI	AlwNI	ApoI	AvaII	BanI	BanII
EbvI	BccI	BceFI	BglI	EmgI	BsaJI	BseMII	BseSI
BslI	BsmAI	BsmFI	Bsp1286I	BsrI	Bst4CI	BstDSI	Cac8I
CjeI	CjeI	CjePI	CjePI	CviJI	CviRI	DdeI	DpnI
BaeI	EcoO109I	EcoRII	FauI	Fnu4HI	FokI	GdiII	HaeI
HaeIII	HhaI	HinfI	HphI	MaeIII	MboII	MnlI	MspI
MspAI	MwoI	NciI	NlaIII	NlaIV	RsaI	Sau96I	Sau3AI
ScrFI	SfaNI	SfcI	StyI	TaiI	TaqII	TaqII	TauI
ThaI	TseI	Tsp45I	Tsp509I	TspRI			

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